

DIFFICULT-TO-DIAGNOSE AND DIFFICULT-TO-TREAT LYMPHOMAS

GRAY ZONE LYMPHOMAS

TREATMENT

Alessandro Broccoli

IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico «Sant'Orsola-Malpighi»
Department of Medical and Surgical Sciences, University of Bologna, Italy
Institute of Hematology «L. e A. Seràgnoli», Bologna, Italy



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Rome

October 15-16, 2026

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Disclosures of Alessandro Broccoli

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Gilead				X	X	X
Merck	X					X
Janssen	X			X	X	X
Takeda		X		X	X	X
Kyowa Kirin	X			X	X	X
Incyte						X
Recordati				X		X
Astra Zeneca				X	X	X
Roche				X		X
GlaxoSmithKline		X		X	X	
BeOne	X			X	X	X
Eli Lilly		X		X		X
SOBI				X		
SERB Pharma		X			X	



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Gray zone lymphoma: moving from histology to clinical management

- The term **gray zone lymphoma (GZL)** is preferred over what was previously designated B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.
- Sequential primary mediastinal large B-cell lymphoma and nodular sclerosis classical Hodgkin lymphoma reinforce the concept of mediastinal GZL, because these diseases have been demonstrated to be of common clonal origin.
- Clinical and genomic data indicate that most patients with **non-mediastinal GZL** are distinct from those with **mediastinal GZL**, and they should be diagnosed as having diffuse large B-cell lymphoma, NOS.

Campo E. *Blood*, 2022; 140: 1229-1253



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PROGNOSIS AND FRONTLINE TREATMENT



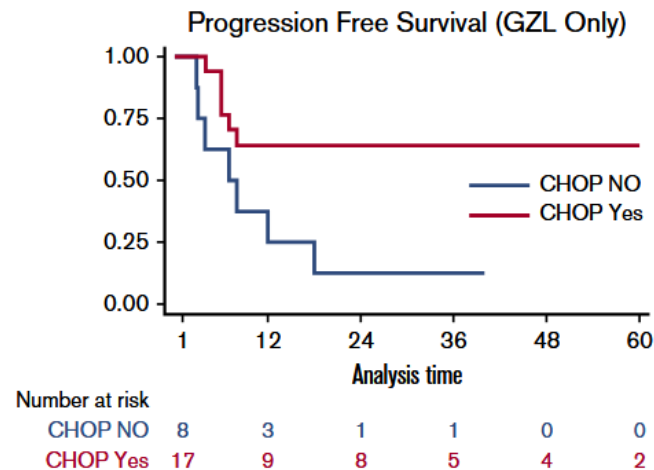
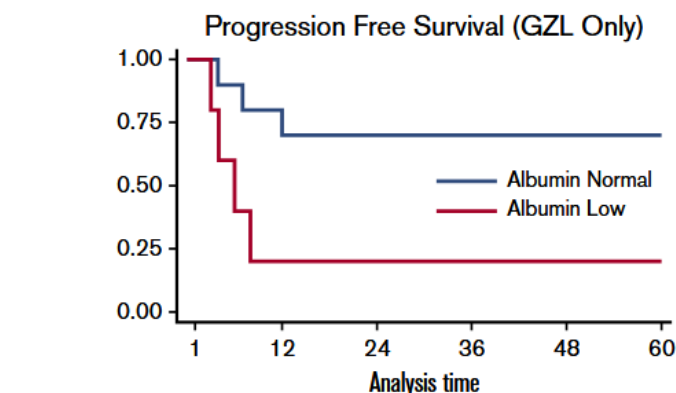
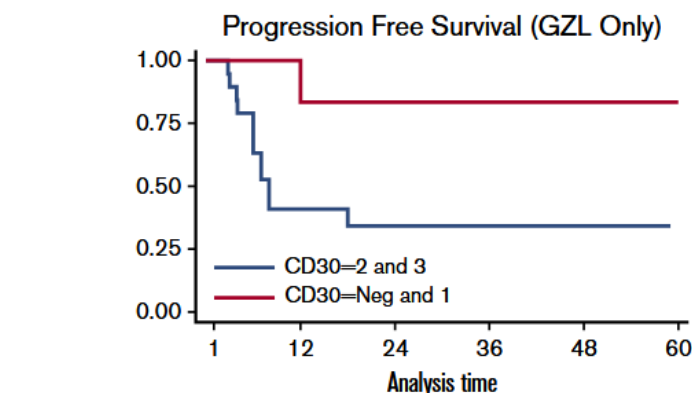
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	4-year PFS			
		95% HR confidence limits		
	HR	Low	High	P
Baseline clinical factors				
Age (continuous)	0.99	0.96	1.03	.75
Sex (male vs female)	0.35	0.12	1.08	.06
B symptoms (yes vs no)	2.47	0.75	8.16	.13
BMI (median)	1.00	0.86	1.16	.99
ECOG performance status (2-4 vs 0-1)	1.40	0.42	4.70	.58
Hemoglobin < 10.5 g/dL (no vs yes)	0.79	0.24	2.61	.70
LDH (creased vs normal)	1.71	0.48	6.16	.40
ESR (increased vs normal)	1.77	0.16	19.63	.63
Albumin < 4.0 g/dL (yes vs no)	5.06	1.11	23.19	.03
Primary mediastinal disease (yes vs no)	0.42	0.14	1.26	.12
Bulky disease (yes vs no)	0.33	0.07	1.53	.15
Stage at diagnosis (1-2 vs 3-4)	0.80	0.25	2.63	.72
Prognostic score, IPI (continuous)	1.28	0.63	2.61	.49
Prognostic score, IPS (continuous)	1.49	0.65	3.42	.34
Treatment factors				
Rituximab (yes vs no)	0.36	0.12	1.13	.08
ABVD (yes vs no)	2.72	0.88	8.42	.08
CHOP (yes vs no)	0.22	0.02	0.53	.008
EPOCH (yes vs no)	6.55	1.28	33.45	.02
Consolidative radiotherapy (yes vs no)	0.36	0.12	1.14	.08

Clinicopathologic consensus study of gray zone lymphoma with features intermediate between DLBCL and classical HL



Pilichowska M. *Blood Adv*, 2017; 1: 2600-2609

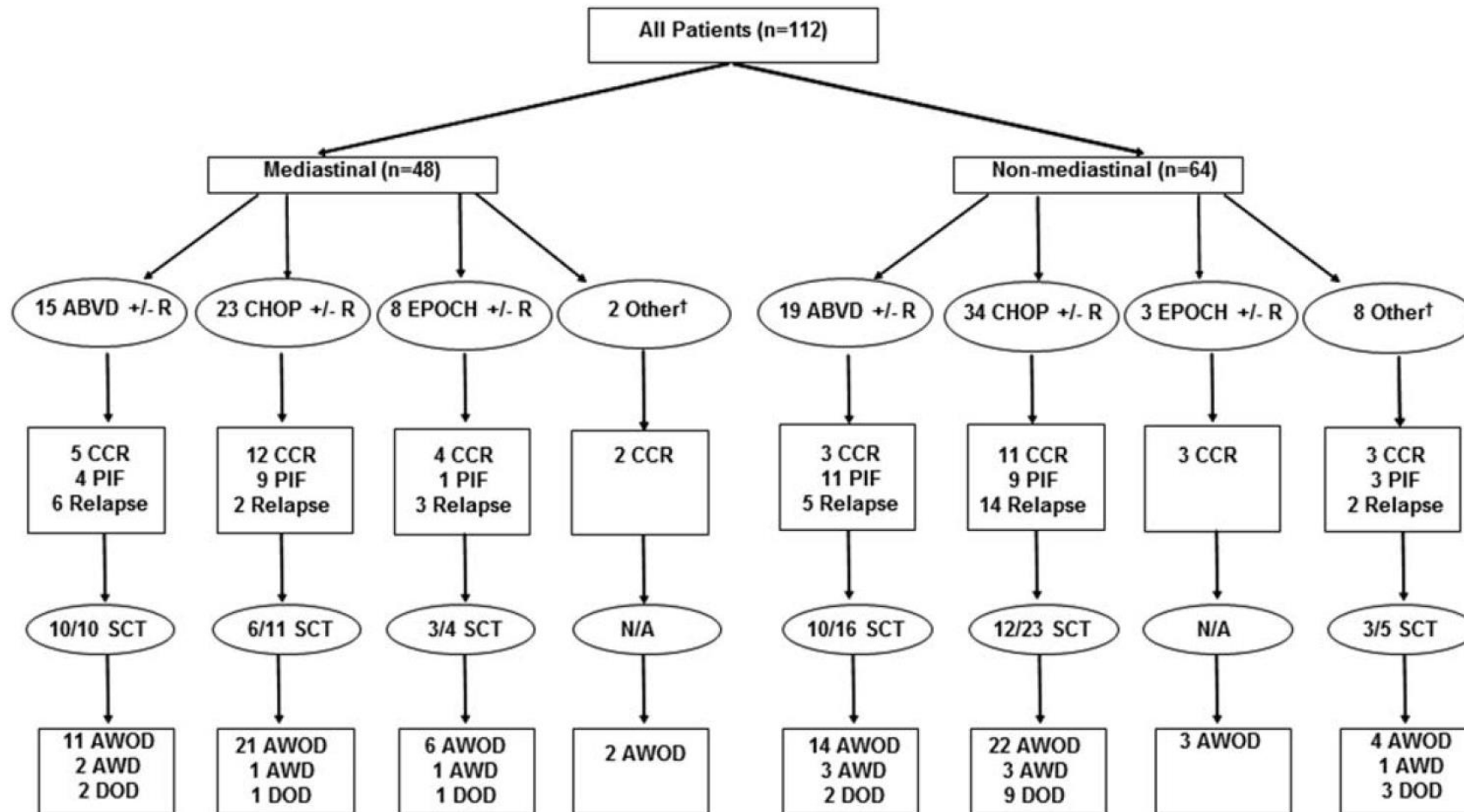


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Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma: Characteristics, outcomes, and prognostication among a large multicenter cohort



Received frontline rituximab: 65%

- with ABVD: 18%
- with CHOP: 91%

ORR: 79/112 (71%)

- with ABVD: 61%
- with CHOP: 71%
- with EPOCH: 82%

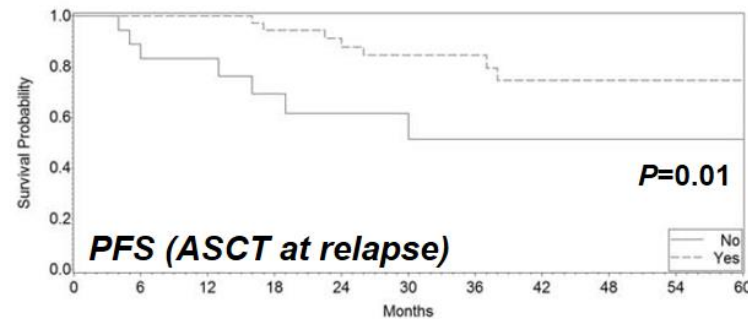
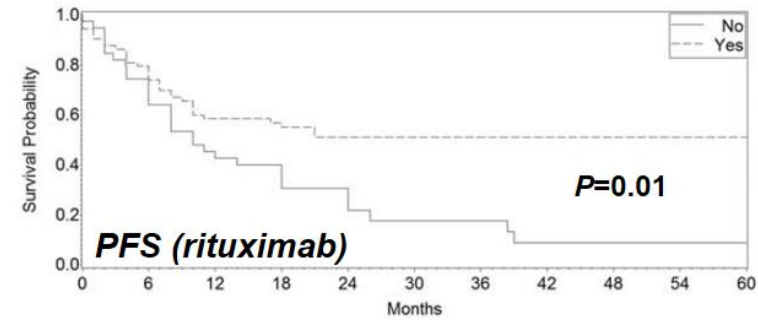
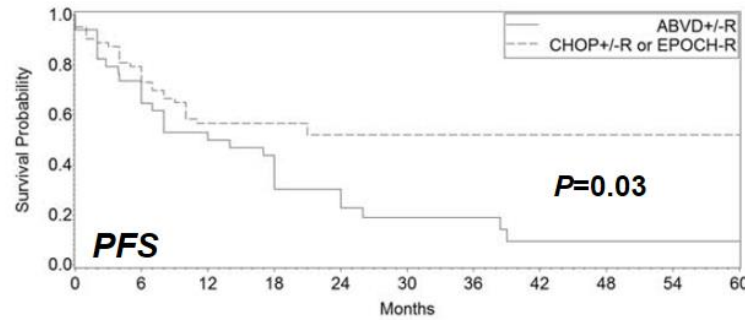
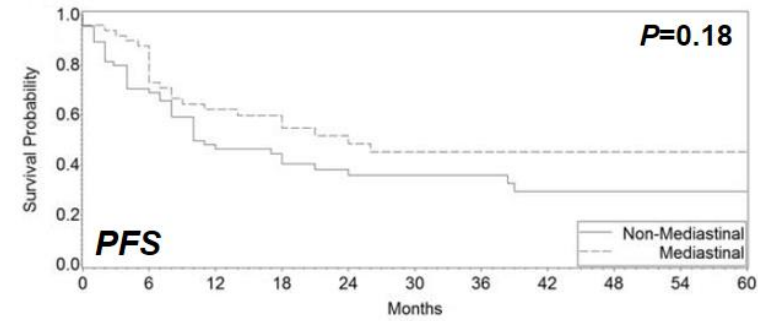
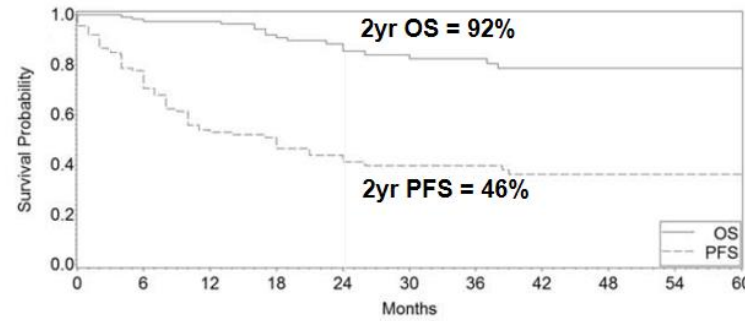
CR rate: 66/112 (59%)

- with ABVD: 55%
- with CHOP: 56%
- with EPOCH: 73%

Primary induction failure (PIF): 33%

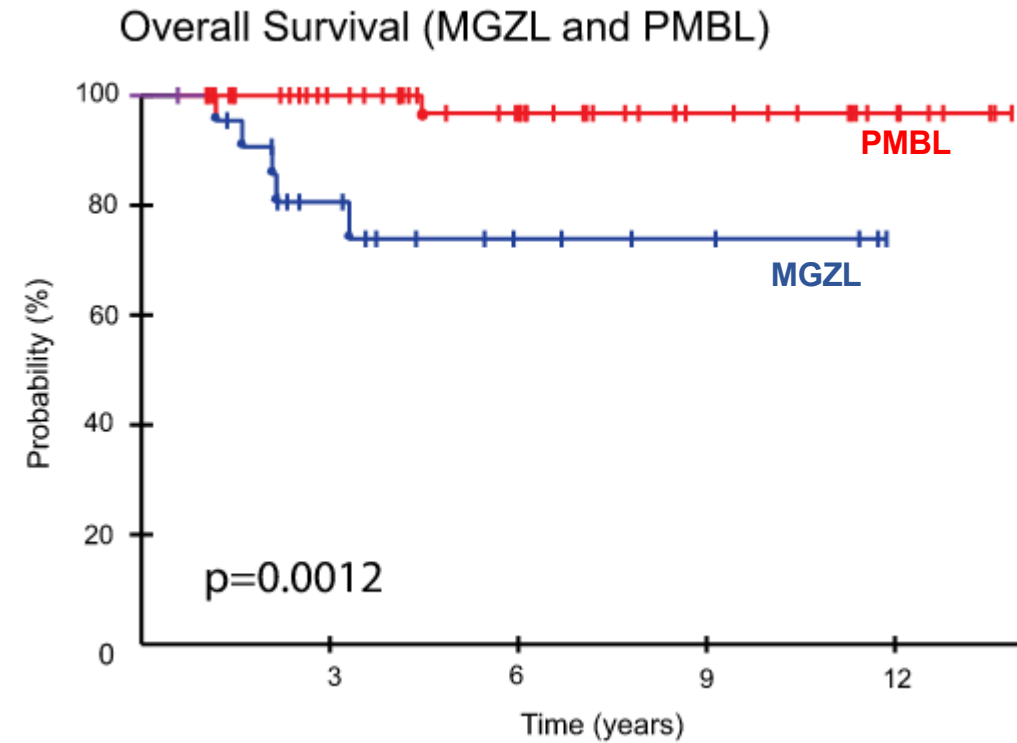
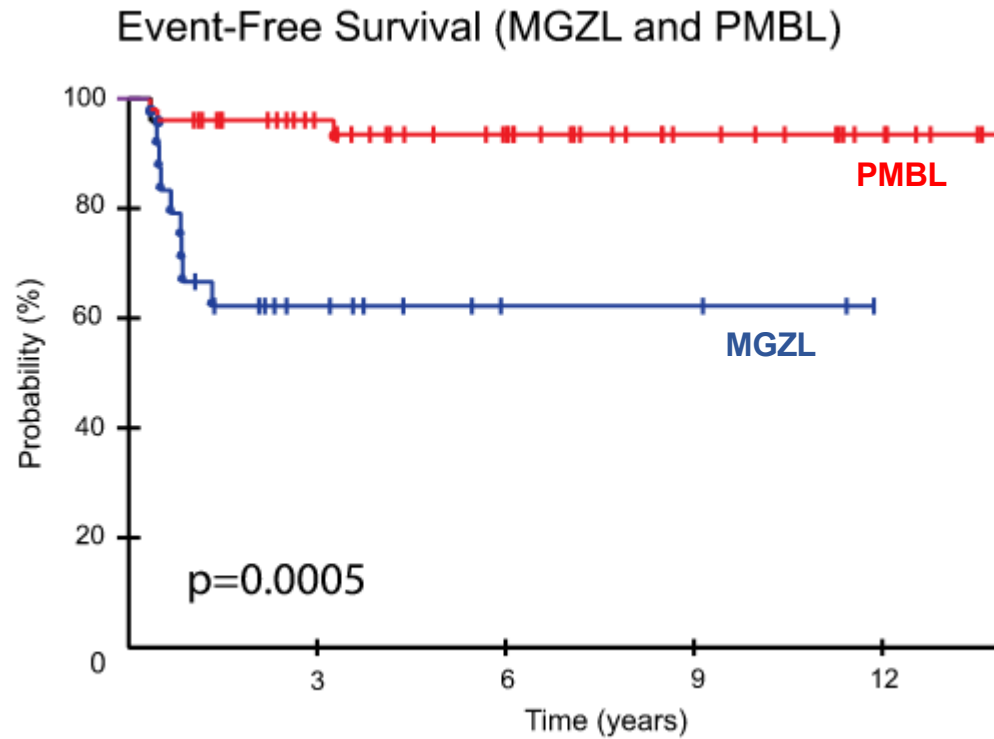
Evens A. *Am J Hematol*, 2015; 90: 778-783

Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma: Characteristics, outcomes, and prognostication among a large multicenter cohort



Evens A. *Am J Hematol*, 2015; 90: 778-783

A prospective study of mediastinal gray-zone lymphoma



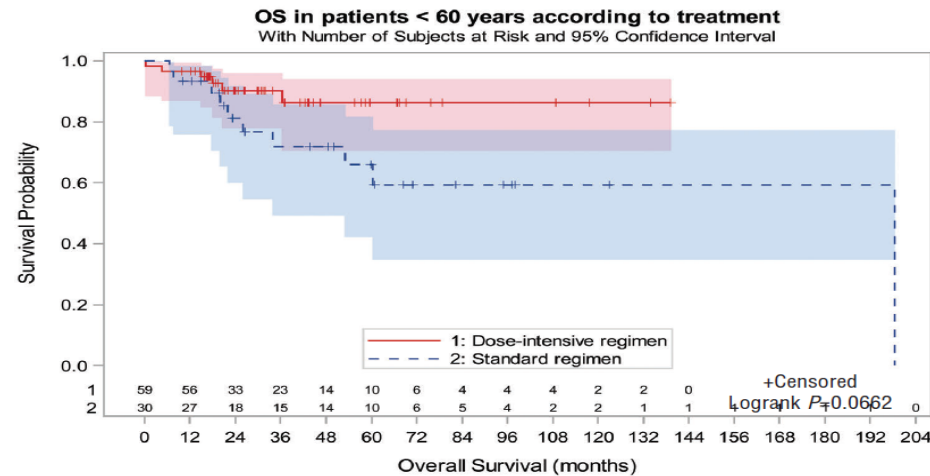
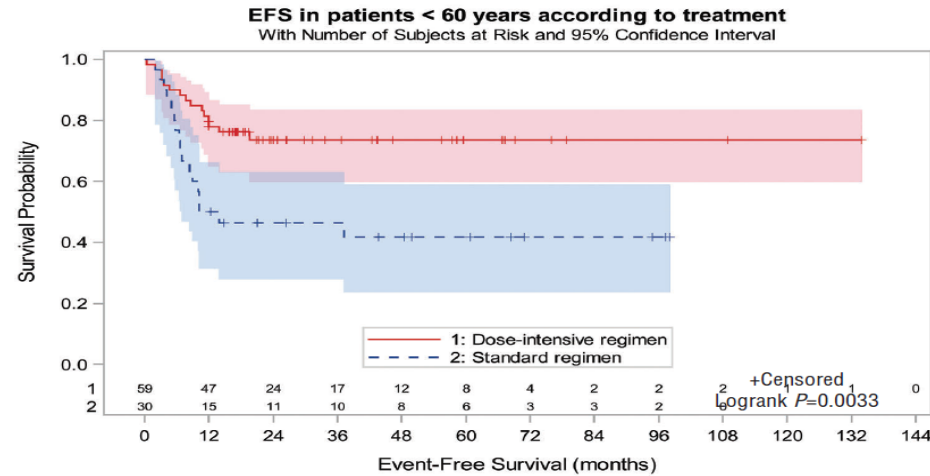
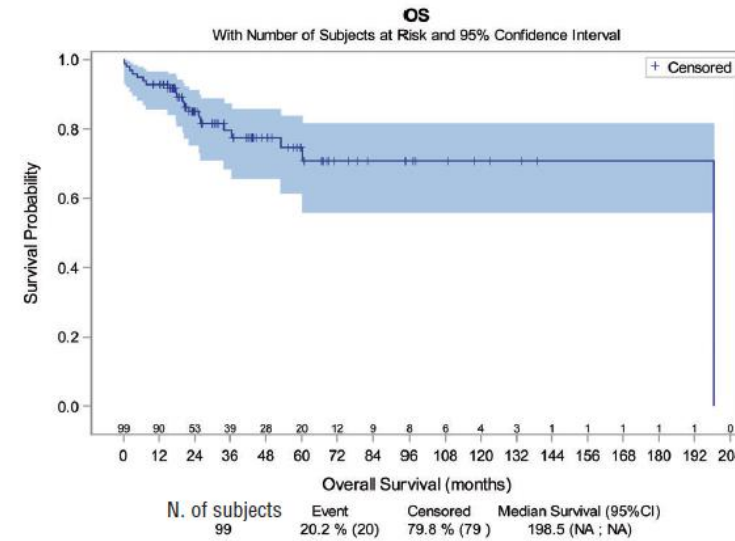
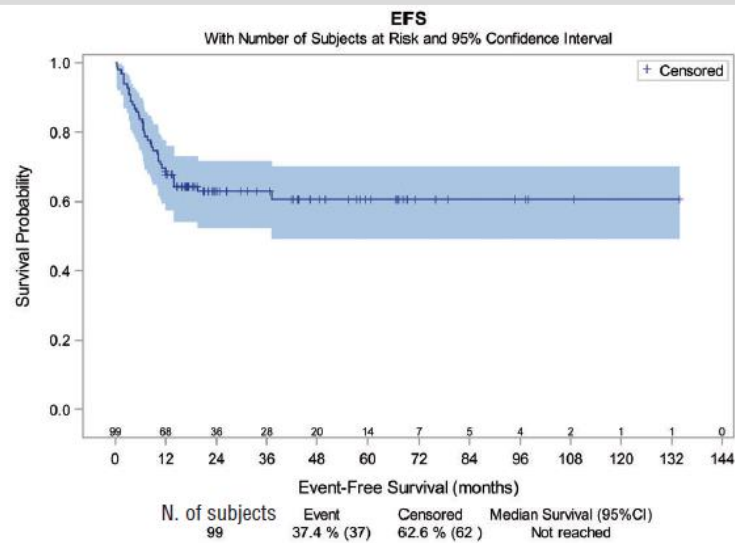
Wilson WH. *Blood*, 2014; 124: 1563-1569

Mediastinal gray zone lymphoma: clinico-pathological characteristics and outcomes of 99 patients from the Lymphoma Study Association

GZL subtype	N (99°)	CR/ PR/ failure / NA		EFS	OS
All	99	72 (73%)/7/19/1°		3y 63% (52-72%)	3y 80% (68-87%)
HL-like GZL	64	49 (77%)/3/11/1		3y 66% (53-77%)	3y 80% (65-89%)
DLBCL-like GZL	30	22 (73%)/1/7/0		3y 63% (43-78%)	3y 75% (52-88%)
Composite GZL	5	1 (20%)/3 /1/0		3y 20% (1-58%)	3y 100%
Treatment	N (98)	CR/ PR/ failure/ NA	χ^2	EFS, <i>P</i> (log-rank)	OS, <i>P</i> (log-rank)
HL-like chemo	42	33 / 2 /7/0	<i>P</i> =0.002*	<i>P</i> =0.004	<i>P</i> =0.13
ABVD	11	5 (45%)/1/5/0		3y 34% (9-62%)	3y 61% (26-83%)
escBEACOPP	31	28 (90%)/1/2 ^s /0		3y 76% (55-88%)	3y 94% (77-98%)
DLBCL-like chemo	56	39/5/12/0	<i>P</i> =0.38**	<i>P</i> =0.18	<i>P</i> =0.19
RCHOP	27	17 (63%)/3/7/0		3y 55% (35-72%)	3y 75% (49-89%)
RACBVP	27	20 (74%)/2/5/0		3y 70% (49-84%)	3y 86% (63-95%)
RCEOP	1	1		—	
R DA-EPOCH	1	1		—	
Rituximab			<i>P</i> =0.38***	<i>P</i> =0.55	<i>P</i> =0.88
With	57	40 (70%)/5 / 12 / 0		3y 63% (49-74%)	3y 80% (65-89%)
Without	41	32 (76%)/2 / 7 / 0		3y 65% (48-78%)	3y 81% (60-91%)

Sarkozy C. *Haematologica*, 2017; 102: 150-159

Mediastinal gray zone lymphoma: clinico-pathological characteristics and outcomes of 99 patients from the Lymphoma Study Association



Dose-intensive regimens (3 yr EFS)
76% escBEACOPP
70% R-ACVBP

Standard regimens (3yr EFS)
34% ABVD
55% R-CHOP

Dose-intensive regimens (3 yr OS)
94% escBEACOPP
85% R-ACVBP

Standard regimens (3yr OS)
61% ABVD
75% R-CHOP

Sarkozy C. *Haematologica*, 2017; 102: 150-159

Efficacy of High-Dose Therapy and Autologous Hematopoietic Cell Transplantation in Gray Zone Lymphoma: A US Multicenter Collaborative Study

Variable	Value
Age, yr, median (range)	38 (18-70)
Sex, n (%)	
Female	11 (34)
Male	21 (66)
Diagnosis, n (%)	
GZL	19 (59)
cHL then GZL on relapse	6 (19)
DLBCL then GZL on relapse	5 (16)
Other	2 (6)
Disease stage at original presentation, n (%)	
I	1 (3)
II	11 (34)
III	13 (41)
IV	6 (19)
Missing/unknown	1 (3)
B symptoms, n (%)	
Yes	20 (63)
No	11 (34)
Missing/unknown	1 (3)
Serum lactate dehydrogenase at presentation, n (%)	
Normal	11 (34)
Elevated	12 (38)
Missing/unknown	9 (28)
Mediastinum involvement at presentation, n (%)	
Yes	23 (72)
No	9 (28)
Bone marrow involvement at presentation, n (%)	
Yes	1 (3)
No	26 (81)
Not performed	5 (16)

Variable	Value
Number of therapies before auto-HCT, median (range)	2 (1-4)
Lines of therapy, n (%)	
1	8 (25)
2	17 (53)
3	4 (13)
4	3 (9)
Induction regimen, n (%)	
ABVD	12 (38)
CHOP-R	9 (28)
EPOCH-R	6 (19)
Other	5 (16)
Remission status at time of auto-HCT, n (%)	
CR1	10 (31)
CR2	9 (28)
CR3	2 (6)
PR1	2 (6)
PR2	5 (16)
PR3	1 (3)
Primary refractory	3 (9)
Cell source	
PBSCs, n (%)	32 (100)
CD34 cell dose, $\times 10^6$ cells/kg body weight, median (range)	4.93 (1.76-18.47)
Conditioning regimen, n (%)	
BEAM	19 (59)
BEAM-R	4 (13)
BEAC	2 (6)
CBV	5 (16)
Other	2 (6)

Kharfan-Dabaja MA. *Biol Blood Marrow Transplant*, 2017; 24: 486-493



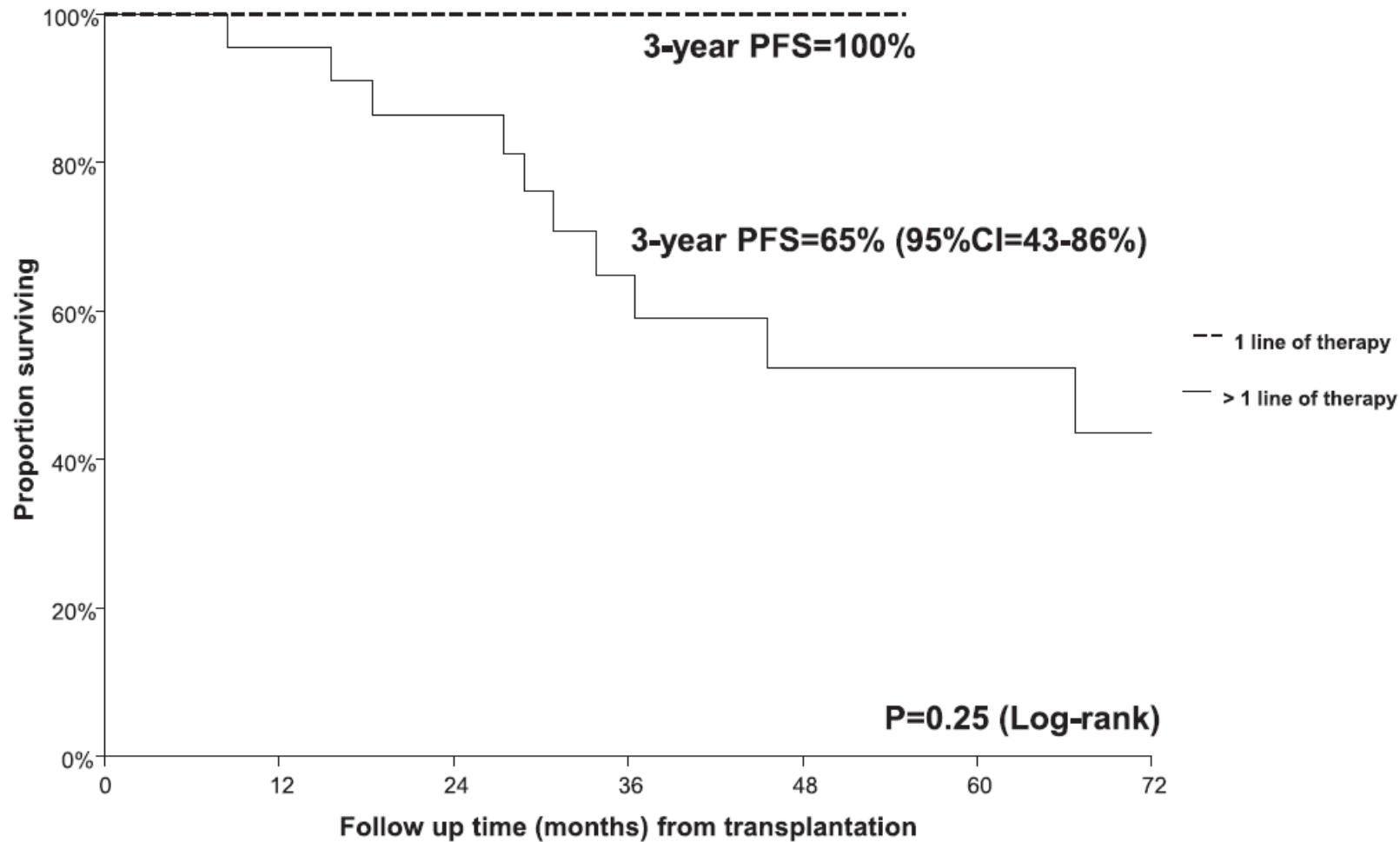
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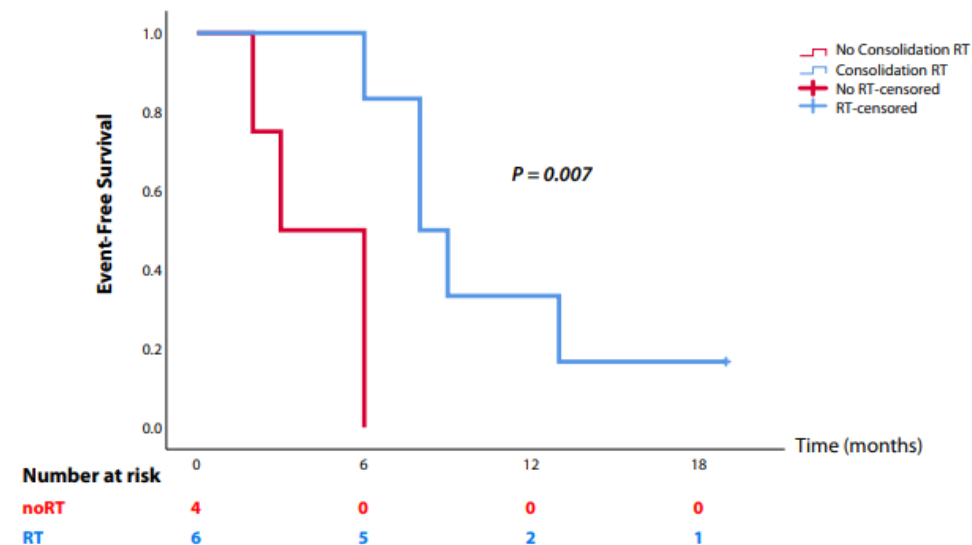
Efficacy of High-Dose Therapy and Autologous Hematopoietic Cell Transplantation in Gray Zone Lymphoma: A US Multicenter Collaborative Study



Kharfan-Dabaja MA. *Biol Blood Marrow Transplant*, 2017; 24: 486-493

The Role of Radiation Therapy in the Management of Gray Zone Lymphoma

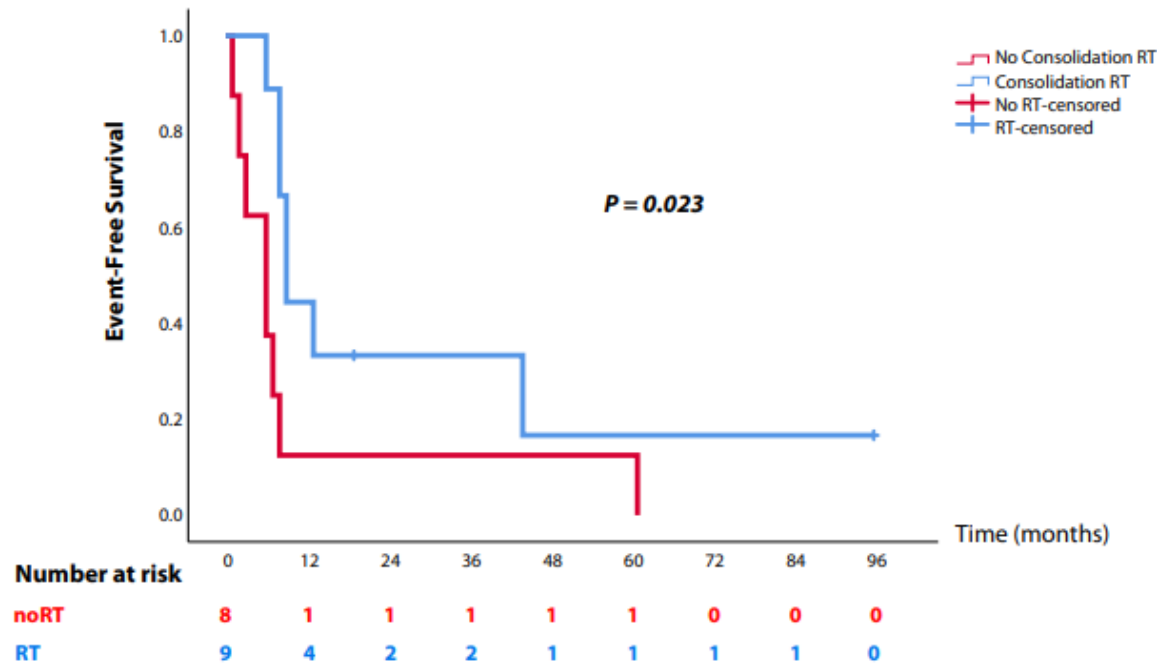
Characteristic	Radiation in the first-line treatment setting			P value
	No (n = 21)	Yes (n = 9)	Total (n = 30)	
Type of chemotherapy				
ABVD	6 (29%)	0 (0%)	6 (20%)	.16
RCHOP	7 (33%)	3 (33%)	10 (33%)	
REPOCH	8 (38%)	6 (67%)	14 (47%)	
Interim response to chemotherapy				
Rapid-early-response	6 (29%)	0 (0%)	6 (20%)	.02
Slow-early-response	8 (38%)	9 (100%)	17 (57%)	
No response	2 (9%)	0 (0%)	2 (7%)	
Not assessed	5 (24%)	0 (0%)	5 (17%)	
End response to chemotherapy				
CR	12 (57%)	3 (33%)	15 (50%)	.03
PR	4 (19%)	6 (67%)	10 (33%)	
PD	5 (34%)	0 (0%)	5 (17%)	
Upfront consolidative RT				
CR		3 (33%)		
PR		6 (67%)		
RT dose (Gy)				
Median (range)		36 (30.6-48.6)		
RT fractions				
Median (range)		20 (10-27)		
EQD2 (Gy)				
Median (range)		36 (30.1-47.8)		
Response to first-line treatment (accounting for upfront radiation)				
CR	12 (57%)	6 (67%)	18 (60%)	.25
PR	4 (19%)	3 (33%)	7 (23%)	
PD	5 (34%)	0 (33%)	5 (17%)	
Subsequent radiation for relapsed/refractory disease				
Peritransplant radiation	4 (19%)	1 (11%)	5 (17%)	.048
Salvage RT	4 (19%)	0 (0%)	4 (13%)	



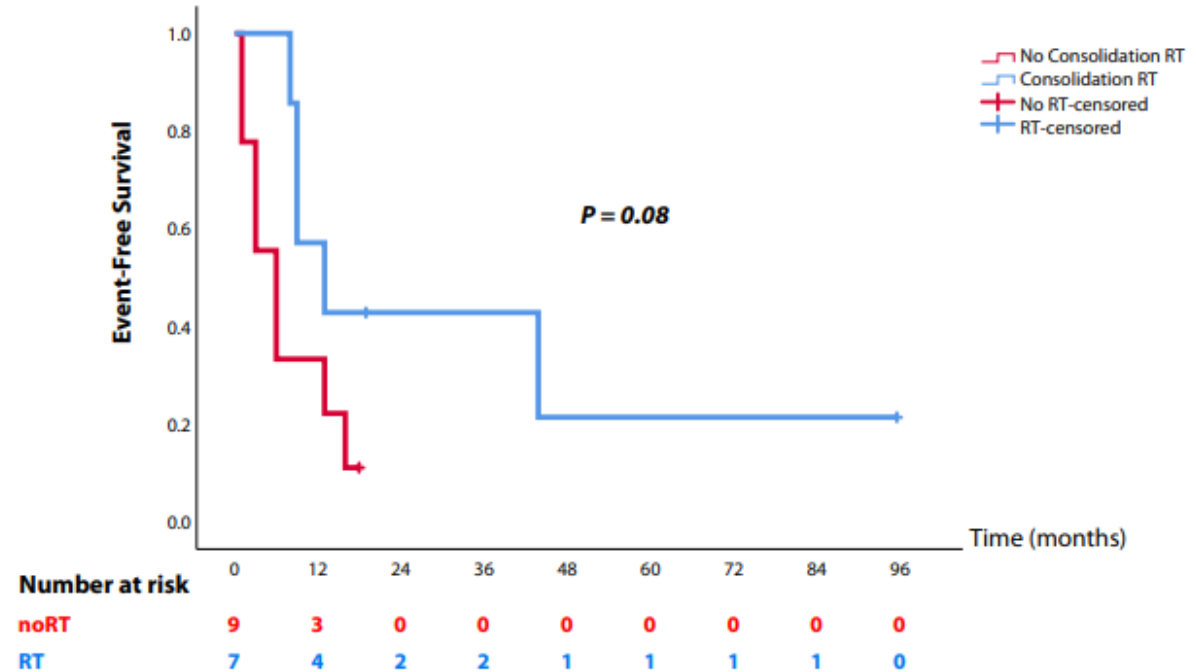
Patients with PR at end of induction

Saifi O. *Int J Radiat Oncol Biol Phys*, 2025; 123: 947-954

The Role of Radiation Therapy in the Management of Gray Zone Lymphoma



*Patients with slow early response to induction
(positive interim PET and no progression)*



Patients with baseline bulky disease

Saifi O. *Int J Radiat Oncol Biol Phys*, 2025; 123: 947-954

RELAPSED AND REFRACTORY DISEASE



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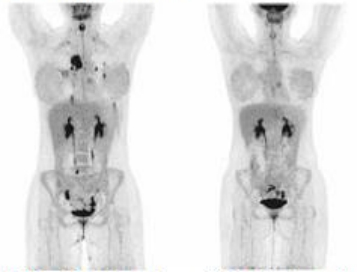
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PD-1 Blockade in Mediastinal Gray-Zone Lymphoma

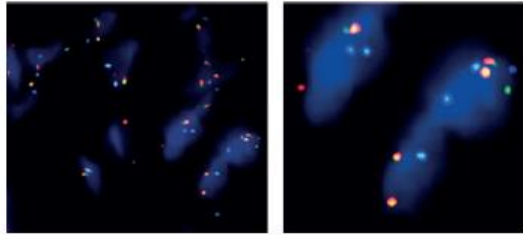
Female, 18 y.o.
DA-EPOCH-R (PR)
Pembrolizumab (CR)
Allo-SCT

A FDG-PET Scans of Patient 1

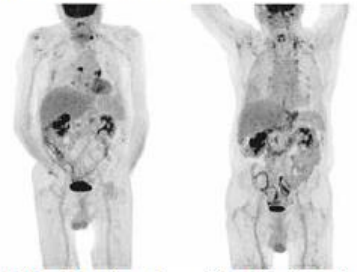


Before Treatment
March 24, 2016 After Treatment
October 20, 2016

B FISH Analysis in Patient 1

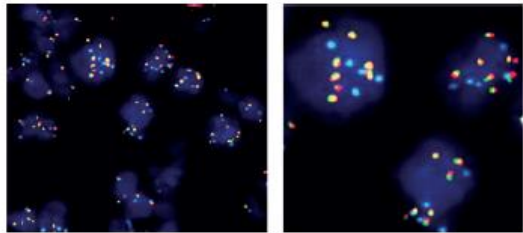


C FDG-PET Scans of Patient 2

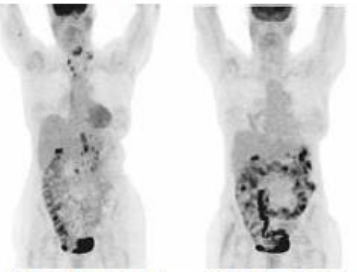


Before Treatment
December 17, 2015 After Treatment
December 15, 2016

D FISH Analysis in Patient 2

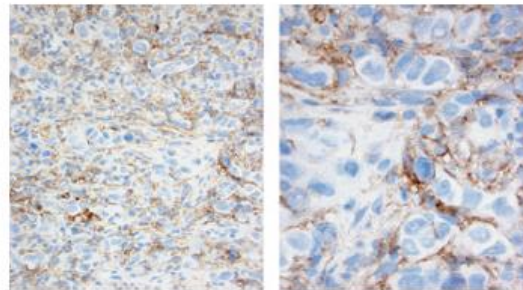


E FDG-PET Scans of Patient 3



Before Treatment
October 21, 2016 After Treatment
January 18, 2017

F Immunohistochemical Analysis in Patient 3



Male, 76 y.o.
Da-EPOCH-R (PR → PD)
Pembrolizumab (CR, +381 dy)

Male, 80 y.o.
DA-EPOCH-R (CR → relapse)
Brentuximab vedotin (PD)
BV+GemOx (PD)
Mediastinal RT (PD)
Nivolumab (CR, +161 dy)

Melani C. *N Engl J Med*, 2017; 377: 89-91

Nivolumab combined with brentuximab vedotin for relapsed/refractory mediastinal gray zone lymphoma

ELIGIBILITY:

- The expansion cohort of the open-label, phase 1/2 CheckMate 436 (NCT02581631) study enrolled pts ≥ 18 years old with ECOG performance status of 0 or 1, and with:
 - confirmed R/R MGZL after autologous hematopoietic cell transplantation (auto-HCT)
 - if ineligible for auto-HCT, after ≥ 2 multi-agent chemotherapy regimens.

SCHEDULE:

- 240 mg nivolumab (on Day 8 of Cycle 1, then Day 1 of following cycles);
- 1.8 mg/kg brentuximab vedotin (on Day 1 of each cycle) every 3 weeks until disease progression or unacceptable toxicity.

Santoro A. *Blood*, 2023; 141: 2780-2783



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Nivolumab combined with brentuximab vedotin for relapsed/refractory mediastinal gray zone lymphoma

Characteristic	MGZL (N = 10)
Age, y	35 (25-72)
>65	1 (10)
Male	6 (60)
ECOG performance status	
0-1	9 (90)
≥2	1 (10)
Refractory disease	7 (70)
Bulky disease >10 cm	3 (30)
Prior systemic cancer therapies, median (range)	2 (1-3)
Prior therapies	3 (30)
R-CHOP	
DA-EPOCHR	4 (40)
Prior auto-HCT	0
Time from completion of most recent prior systemic therapy to study treatment, mo	
<3	8 (80)
3-6	1 (10)
>6	1 (10)

- Ten patients treated and evaluable.
- All patients had a mediastinal mass.
- Median of 2 prior lines of systemic cancer therapy; no prior auto-HCT.
- Eight months after the last patient received the first treatment, all patients had discontinued treatment: 5 due to disease progression, 4 due to allogeneic-HCT, and 1 due to auto-HCT.
- Patients received a median of 7 doses of nivolumab and 7 doses of brentuximab.

Santoro A. *Blood*, 2023; 141: 2780-2783



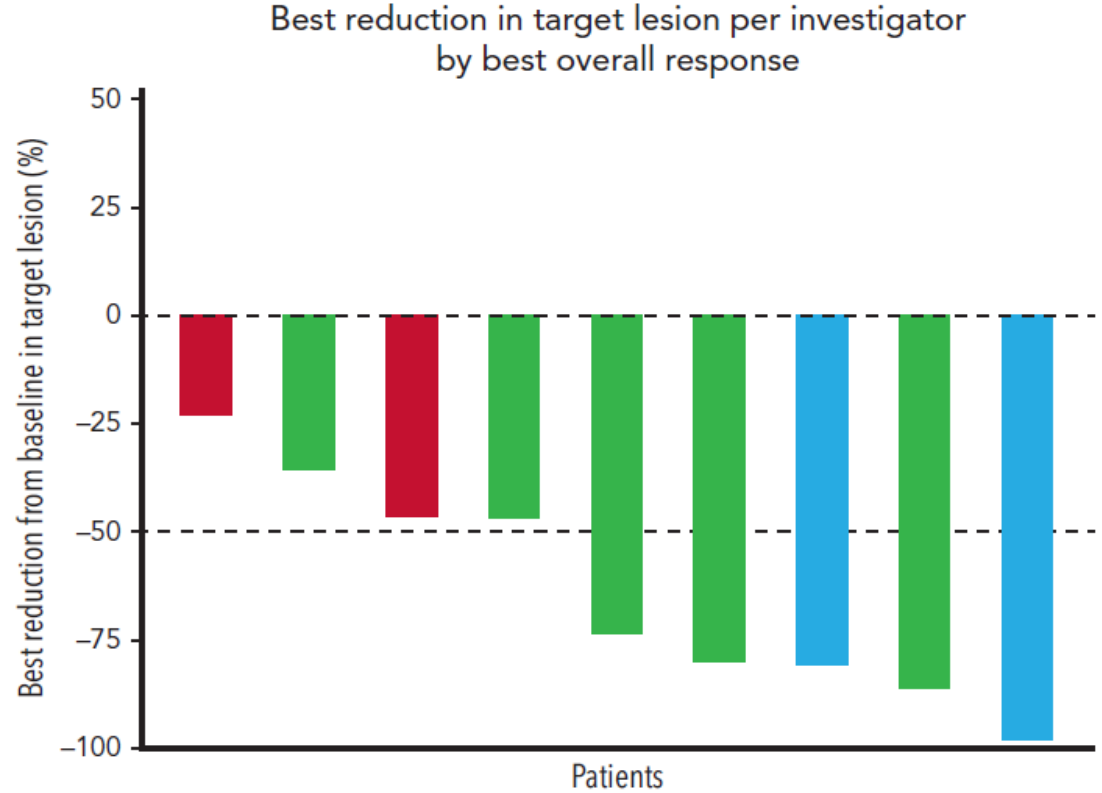
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Nivolumab combined with brentuximab vedotin for relapsed/refractory mediastinal gray zone lymphoma



Response evaluable patients are those with target lesion(s) assessed at baseline and with all baseline target lesion(s) assessed at > 1 on-study timepoint. Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy.

Complete response Partial response Stable disease Progressive disease

Best overall response per investigator (Primary endpoint)

Best overall response	MGZL (N = 10)
Objective response rate, % (80% CI)	70 (45–88)
Complete response	5 (50)
Partial response	2 (20)
Stable disease	0
Progressive disease	2 (20)
Death prior to disease assessment	1 (10)

Data are n (%) unless stated otherwise.

Santoro A. *Blood*, 2023; 141: 2780-2783



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Nivolumab combined with brentuximab vedotin for relapsed/refractory mediastinal gray zone lymphoma

- The time to CR was 1.2-4.8 months and the duration of CR was 1.5-3.2 months before pts were censored for subsequent therapy.
- The 5 patients who achieved CR were bridged to hematopoietic cell transplantation (4 allo- and 1 auto-HCT) and censored (all alive at database lock).
- At a median follow-up of 12.4 (range, 0.1-25.5) months:
 - 6-month OS rate: 80.0% (95% CI, 40.9-94.6); median OS not reached.
 - Median PFS 21.9 months.
 - DOR could not be estimated due to earlier censoring of CR pts who received subsequent therapies.
- Nine pts (90%) experienced any grade treatment-related adverse events:
 - neutropenia (n = 3; 1 grade 1, 1 grade 2, 1 grade 3 event);
 - paresthesia (n = 3; all grade 1);
 - 3 patients (30%) with grade 3-4 TRAEs.
- A serious drug-related AE occurred in 1 elderly pt (grade 3 febrile neutropenia).
- Three deaths, all caused by disease progression.

Santoro A. *Blood*, 2023; 141: 2780-2783



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Take home messages

- A hard to diagnose disease, with overlapping features between classic Hodgkin lymphoma and primary mediastinal lymphoma and high morphologic variability.
- Peculiar mutational landscape, dichotomy between “mediastinal” and “non-mediastinal” forms.
- Immune-escape immunohistochemical signature.
- Unknown best frontline approach. Inconclusive data supporting more intensive first line therapy.
- Autologous stem cell transplantation performs well in first complete remission and also as salvage approach.
- Checkpoint inhibitors (anti-PD1 antibodies) have a role in relapsed and refractory disease. Unknown role in frontline therapy.
- Combination of anti-PD1 and anti-CD30 (nivolumab + brentuximab) recently explored, deserves further investigation.